

Newsletter

Society For Medicines Research

SMR



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Dr Geoffrey Stemp: New SMR Chairman

Dr Geoffrey Stemp has taken over as the Chairman of the Society for Medicines Research.

He joined the Society in 1980, becoming a member of the Committee in 1994 and serving as Honorary Treasurer from 1998 - 2000.

Dr Stemp joined Beecham Pharmaceuticals as a medicinal chemist at the research site at Harlow, Essex in 1979. Since then he has gained experience in the gastrointestinal, cardiovascular and CNS disease areas.

He is currently a Director of Medicinal Chemistry within the Neurology and GI Centre of Excellence for Drug Discovery at GlaxoSmithKline.

Notice to Members

Look out for your membership renewal form that will arrive in February. Please ensure all your contact details are up to date and you pay your subscription promptly. Any questions, Email Lilian at the secretariat.

secretariat@socmr.org

We are always willing to consider unsolicited items for publication in the newsletter - we encourage you to submit articles that would be of interest to the SMR membership. In the first instance send them to secretariat@socmr.org

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Membership News

New Members from October 2003

| NAME | ORGANISATION |
|--------------------|---------------------------------------|
| Dr K A Frimat | Exchem Organics, Colchester, Essex |
| Mr D A Rivers | GlaxoSmithKline, Herts |
| Mrs J B H Warneck | Amedis Pharmaceuticals Ltd, Cambridge |
| Dr R Pettipher | Oxagen Ltd, Abingdon |
| Dr T W Hart | Novartis, Cambridge |
| Dr L Gazi | Oxagen Ltd, Abingdon |
| Dr S L Gyles | Oxagen Ltd, Abingdon |
| Dr A Missio | Max-lebsche-Platz, Munich, Germany |
| Dr B Bang Anderson | H.Lundbeck A/S, Denmark |
| Dr D Michalovich | Inpharmatica Ltd, London |
| Dr D Naughton | University of Brighton |

Where are they now? We need your help.....

Below is a list of SMR members who we no longer have the correct address for. Please take a moment to read through and if you know where any of them are could you either contact the secretariat or ask them to, so we can update our membership list and include them in our mailings. Thank you for your help

| | | | |
|---------------------|------------------|------------------|------------------|
| Dr A R Ali | Dr T Eaves | Mr D F Lewis | Dr D Selwood |
| Dr D J Barlow | Dr A C Flind | J G Maconochie | Mr M H Shah |
| Dr M G Bird | Dr C D Floyd | Dr B J Meakin | Dr C Southan |
| Dr R G Boyle | Dr I François | Dr J Mercer | Dr P D Stonier |
| Dr R Brimblecombe | Dr Fraser | Dr G Metcalfe | Dr L Surh |
| Dr M J Broadhurst | Dr D Haigh | Dr S Miah | Mr J Turner |
| Dr H Broughton | Dr N M Hamilton | Miss M Miller | Dr M S Tute |
| Dr J B Buckton | Dr S L Hart | Dr P K Moore | Dr M B Tyers |
| Dr S F Campbell | Dr H J Herdon | Dr G J Murphy | Ms Vernon-Wilson |
| Dr Christie | Dr S C Hirst | Dr D Neuhaus | Dr T Ward |
| Ms J W Christie | Dr M R Huckstep | Dr U M Ney | Dr R W Ward |
| Mr Y-K Chung | Dr P Huxley | Dr M S Nobbs | Dr Warrellow |
| Dr M S G Clark | Dr F Ince | Dr R A O'Donnell | Dr J G Whateley |
| C J Clements | Dr R G Jackson | Dr L J Payne | Dr A W Wheeler |
| Dr M P Coghlan | Dr S Jenkinson | Dr M C Pritchard | Dr M Whittaker |
| Dr I Collins | Dr R C F Jones | Dr D Rees | Dr D Wu |
| S M Cooper | Mr S J Jones | Dr Reynolds | |
| Dr M Courtney | Dr H H Khodr | Dr D M Ricketts | |
| Prof. J Crossland | Dr L J S Knutsen | Dr M Rowley | |
| Dr J M Dewdney | Dr S P Langston | Dr N Saghir | |
| Dr B Domayne-Hayman | Dr C A Leach | Dr F H Sansbury | |
| Dr M J Drysdale | Dr N Lench | Dr Scopes | |

Trends in Early Drug Safety By Richard E. Armer and Ian D. Morris

Report from our September 2003 Meeting

Drug safety is an essential and integral component of the preclinical development of any new medicine. Recent high profile withdrawals of drugs from the market place such as cerivastatin and the continued loss of development compounds for toxicology reasons have highlighted the need to address drug safety earlier and more effectively in the discovery and development timeline.

On September 18th, 2003, the Society for Medicines Research held a one-day meeting entitled Trends in early Drug Safety. The meeting brought together speakers from the UK representing both academia and industry and provided an overview of the latest trends in the application of safety studies within pharmaceutical research and development. The three main themes of the meeting were: 1) General safety and P450 mediated safety issues; 2) New opportunities in drug safety; and 3) Clinical and Regulatory aspects.

Dr. Mark Graham (Safety Assessment, AstraZeneca R&D Charnwood, Loughborough, U.K.) gave an overview and examples of the current application of drug safety studies within early research at AstraZeneca. The basic aim of the 'discovery toxicologist' is to provide a "package" of *in vitro* and *in vivo* data, which is designed to evaluate the risk of exposing people to the compound under development. This package contains information on the potential target organ toxicities, the reversibility of the lesions, the characteristics of the dose-response curves and, consequently, sensible plasma exposure levels to aim for in the clinic. If the risk is considered acceptable, the compound will progress into the clinical stages of development. The fact is that roughly 40% of new drug candidates fail at the preclinical stage. Given that drug development becomes exponentially more expensive as the project progresses, there is obviously an urgent need for reliable, predictive safety screens, which can be applied early during the drug discovery process. A wide variety of information is available, including *in silico* databases, structure-activity screens, specific *in vitro* screens, e.g. for genetic toxicity and safety pharmacology parameters, and *ex vivo* and *in vivo* assays, but the fact that so much attrition still occurs suggests that there is considerable room for improvement.

There is regulatory guidance as to what preclinical studies are required to support the various stages of clinical development, but there is also leeway for the toxicologist to design studies appropriate for the project in question. Typically, prior to first dose to man, cardiovascular, CNS and respiratory safety pharmacology studies, *in vitro* and *in vivo* genetic toxicology, acute toxicity studies in rats and mice and subacute (up to 1

month duration) toxicity studies in a rodent and a non-rodent species, will have been completed. Where possible, the proposed clinical route and schedule of administration will be taken into account in the study design. As clinical trials progress to longer-term studies, the toxicology studies required to support them are also of longer duration such that by registration, studies of six months duration in rats, nine or twelve months in dogs and lifetime carcinogenicity studies in rats and mice will have been completed. A programme of reproduction toxicology is also included to support later clinical trials and registration.

Dr. Nick Plant (Molecular Toxicology, School of Biomedical and Molecular Sciences, University of Surrey, Guildford, UK) reviewed the cytochrome P450 enzymes and their role in drug safety. It is a well established that there exists inter individual variation in the expression of all 50 or so CYP proteins within the human body. Whereas such variation provides us with our uniqueness, it also presents a potential problem for the development and administration of therapeutic compounds. In addition to this inherited variation it is also clear that drugs alter the levels of enzymes within the body, causing either induction or inhibition of drug metabolizing enzymes. However, in situations where individuals are exposed to multiple inducing compounds, the potential for drug-drug interactions arises. Induction/inhibition of drug metabolizing enzymes by one drug may alter the effects of a second, potentially leading to loss of efficacy or increased adverse side effects.

To study the role of both genetic and environmental factors in determining cytochrome P450 levels in an individual, two examples of CYPs involved in the metabolism of therapeutic compounds were described: CYP2D6 and CYP3A4. Both enzymes are susceptible to induction/inhibition of activity by drugs, which can result in clinically significant drug-drug interactions. CYP2D6 activity also has a clearly defined genetic component, with approximately 7-10 % of Caucasians being classed as 'poor metabolisers'. Such an established effect clearly demonstrates the need to incorporate this into the safety assessment of novel compounds. In contrast, CYP3A activity levels show a marked inter individual variability, yet no polymorphisms within the CYP3A4 gene have been identified that could account for the majority of this variability. The role of polymorphisms in other CYP3A enzymes and the transcription factors that control CYP3A4 expression may however shed some light on the observed inter individual variation.

Dr. Barry Jones (Pharmacokinetics Dynamics and Metabolism, Pfizer Global Research and Development, Sandwich, UK) outlined the characteristics of the cytochrome p450 enzymes and their structure activity relationships. The major human CYPs can be characterised in terms of their substrate selectiveness as: CYP1A2: Neutral or basic lipophilic planar

molecules with at least one putative H-bond donating site. A good example of a xenobiotic substrate is theophylline.

CYP2D6: Aryl-alkyl-amines (basic) with site of oxidation a discrete distance from protonated nitrogen. Substrates are lipophilic, particularly when measured or calculated for the neutral form. Principle substrates are β -adrenoceptor blockers, Class I anti-arrhythmic and tricyclic anti-depressants. Often hydroxylation occurs in an aromatic ring or an accompanying short alkyl side chain.

CYP2C9: Neutral or acidic molecules with site of oxidation a discrete distance from H-bond donor or possibly anionic heteroatom. Molecules tend to be amphipathic with a region of lipophilicity at the site of hydroxylation and an area of hydrophobicity around the H-bond forming region. Principal substrates are non-steroidal anti-inflammatory agents. Oxidation often occurs in an aromatic ring or an accompanying short alkyl side chain.

CYP3A4: Lipophilic, neutral, or basic molecules with site of oxidation often nitrogen (N-dealkylation) or allylic positions. This CYP metabolises a wide range of substrates covering all types of pharmaceuticals.

CYP2E1: Small (molecular weight of 200 daltons or less) normally lipophilic linear and cyclic molecules. Volatile anaesthetics are a good example for this isozyme. It is noteworthy, however, that there are many exceptions to these broad rules and CYP's represent the ultimate in promiscuous enzymes.

By definition all substrates of P450 have the ability to act as competitive inhibitors. Some compounds, known as "mechanism based inhibitors", are activated to meta-stable or stable complexes during metabolism and become irreversible or slowly reversible inhibitors. Potent inhibitors of P450 often include a nitrogen containing heterocycle (pyridine, imidazole or triazole) capable of forming a lone pair ligand interaction with the haem of P450. The ligand interaction contributes some 6 Kcals of binding energy to the interaction (3 order of magnitude increase in potency as an inhibitor). Although such heterocycles are essential for the activity of certain drugs (azole antifungals: 14-alpha demethylase inhibitors) their incorporation into molecules is commonplace to increase solubility. Medicinal chemists have responded to metabolism by CYP's in a variety of ways, for example, reducing lipophilicity or incorporating stable functionality (halogens, cyclopropyl groups, and primary or secondary amines) to attenuate or block metabolism.

Prolongation of the QT interval measured on the electrocardiogram is associated with life threatening arrhythmias. The risk of QT prolongation by new therapeutic entities is of particular interest to regulators world-wide and was discussed by **Dr. Leslie Patmore** (Vice President, Preclinical Safety and Efficacy, Quintiles Ltd, Heriot Watt University Research Park, Edinburgh, UK). QT prolongation has contributed towards the withdrawal from the market (e.g. Terfenadine, Cisapride, Terodiline) or labelling restrictions

imposed on current products (e.g. Pimozide). The EMEA has indicated more in depth testing of cardiac toxicity should be conducted before clinical trials. A guidance document ICHS7B is at a late draft stage. The current version indicates that the risk of QT prolongation in new therapeutic entities should be evaluated on 4 different levels:

- Theoretical assessment based on pharmacological/chemical class
- Interactions with IKr or HERG channel
- Repolarization assay (e.g Purkinje fibre)
- QT measurement *in vivo*

Quintiles has experience in performing these assays, particularly rapid HERG screening and has invested in the latest technology amenable to HTS (fluorescence and Rb flux) and automated patch clamping. Repolarization assays present issues, for example, differences in species sensitivity to IKr blockers, as well as sex differences. What may not be forthcoming is a correlation of *in vitro* (e.g HERG block) and *in vivo* (QTc) assays. Predictions are not easy. What is clear is that compounds that block HERG do not necessarily prolong action potential or QT, and compounds which do not block HERG can prolong cardiac action potential. Some HERG blockers shorten the action potential. Quintiles are using these methods to support the development of new drugs and to assist in candidate selections. They have established a considerable database on the outcome of these studies. In an overview of industry practice, a 2002 survey of emerging practices in safety pharmacology showed that from 33 responding companies, most included HERG, repolarization and *in vivo* QT studies, indicating that the ICHS7B guidelines are being adopted ahead of finalization of the document.

Dr. Jonathan Tugwood (Molecular Toxicology Group, Safety Assessment Dept., AstraZeneca Pharmaceuticals, Macclesfield, UK) introduced an approach to early identification of toxic potential of compounds using gene chip technology to perform transcript profiling. In this regard there are two main applications of this toxicogenomic technology: i) to assist with mechanistic investigations of drug toxicity ("problem solving"), and ii) the construction of gene expression databases as a means of developing potential predictive tools, that can be used to assist compound selection decisions early in the Discovery process.

The development and application of gene arrays, comprising large collections of genes from a number of species, has facilitated experimental effort in both these areas. The presentation provided illustrative examples of applications using the rat Affymetrix chips which can provide information on over 25,000 genes. Specifically, investigative work aimed at understanding the corneal toxic effects of a class of novel anti-cancer agents (EGFR tyrosine kinase (TK) inhibitors) was discussed. Studies using phospho-specific antibodies

demonstrated that the toxicity was unlikely to be due to inhibition of EGFR TK in the cornea. It was suggested (not proven) that kinases compensating for the inhibition of EGFR TK may also be inhibited causing the toxicity. This approach allowed the identification of gene clusters specially associated with the pharmacology or toxicology of the compounds underdevelopment. Interestingly these clusters were not necessary consistent between the different chemical groupings. This approach is expensive and has led to a multi-company collaborative strategy towards developing a rat toxicity transcript profile database. The results from 225 studies, using 10,000 gene chips providing 260 million data points, are now available to this group giving hope of predictive *in vivo*, drug-induced toxicology.

Dr. Elaine Holmes (Biomedical Sciences, Imperial College London, U.K.) presented the evolving area of metabonomics and its potential application to study human toxicological events. Metabonomics provides a non invasive systems approach to measuring dynamic biochemical responses of organisms to pathological stimuli or genetic modification and operates by profiling the metabolic responses of key intermediary biochemical pathways. Metabonomic technology, coupling sophisticated analytical methods such as high resolution ¹H NMR spectroscopy or mass spectrometry with appropriate chemometric strategies, enables simultaneous measurement of a wide range of metabolites in biofluids or tissues in a dynamic manner. Such analysis has been shown to be of considerable value in providing detailed information regarding the metabolic status of an organism and in characterizing and predicting a wide range of pathological conditions. Models of site or mechanism-specific toxicity can be constructed and combined to form predictive expert systems for toxicity screening. The complexity and interactive nature of biological systems introduce confounding variation into the metabonomic data. Various chemometric and bioinformatic strategies for optimizing the characterization and prediction of pathological conditions can be adopted in order to increase the sensitivity of metabonomic analysis. Using such sensitive technology, it is often possible to improve the efficiency of drug toxicity screening and lead candidate selection.

Dr. Paul Rolan (Medeval, Manchester Science Park, Manchester, UK) gave an overview of the options to be considered to ensure a first safe entry of a drug into man. The safety of a drug can be defined as the difference between the dose-concentration-response relationships for target pharmacology and toxicology or non-target pharmacology. Maximum tolerated doses (MTDs) are often sought in first in man studies but this can often be inappropriate (e.g. with anticoagulants, insulin) and as the MTD may be orders of magnitude higher than the effective dose, safety/efficacy biomarkers may replace it as an endpoint. The 'safety' of a

study is defined as achieving the study objectives with minimum likelihood of clinically important adverse events. Key predictive methods include the use of animal data, tests on human material *in vitro*, observation of desired pharmacological effect, effects of other similar compounds and any natural or unnatural phenotypes that may be available. The basic premise behind animal safety studies is that large doses of drug given to small numbers of animals will predict likely human toxicities. However, with an increasing proportion of potential new medicines coming from biotechnology e.g humanised antibodies, such a scientific premise is unlikely to be correct. Similarly, the long-term biological consequences of potential therapies such as DNA vaccines, cellular (e.g. stem cell) therapeutics and immune modifiers may be uniquely human. Even for conventional small molecules many problems can occur e.g. species variability (triptans appear toxic in dogs but are safe in humans), population homogeneity (in-bred lines of laboratory rats can give very specific responses not representative of the general species). For some types of organ toxicities (e.g. behavioural toxicities such as cognitive or perceptual impairment) it may be difficult to detect effects in animals and sometimes the desired pharmacology may mask a toxic event. Prediction of hepatotoxicity is notoriously poor from animal studies.

It is more difficult to be confident of detecting toxicities not associated with the primary pharmacology. Traditionally, we have sought clear endpoints such as histological damage. However, such damage is at the end of a spectrum of drug effects and it is often difficult to make predictions about the safety of low doses in man based on toxicity in a few animals at high doses.

Non-invasive biomarkers, which could detect early drug-related injury predictive of clinical toxicity, would be of great interest. Such biomarkers are likely to be system- rather than drug-specific and makes their development unattractive to the pharmaceutical industry and incompatible with the therapeutic area specialisation. Although there is cross-company collaboration in the validation of biomarkers for efficacy (e.g. Osteoporosis Consortium) there is less effort with potential safety biomarkers.

The best current practice is for the clinical pharmacologist to be closely involved with the preclinical programme. To generate a good investigator's brochure ensure that desired and undesired effects are related to concentration; use all sources of prior knowledge; increase use of biomarkers; don't always seek a 'maximum tolerated dose'; observe carefully and most importantly think clearly.

Dr. Rashmi Shah (Medicines and Healthcare products Regulatory Agency, Nine London, UK) completed the symposium with personal view of some of the issues that face regulatory authorities today. The key questions the regulator asks of a new drug are (1) does it work? and (2) is it safe? The

overall aims being to improve public health. Evaluation of these points involves a measure of the risk/benefit profile of any drug dependent on dose, potential co-medication interactions and effects based on the ethnicity or genotype of the patient. Between 1990 and 2001 in the UK 23 drugs were withdrawn - 5 for hepatotoxicity, 7 for QT prolongation, 1 for drug-drug interactions, 2 for a combination of QT prolongation and drug-drug interactions and 8 for other reasons. Interestingly, between 1960 and 1999 of 87 out of 121 drug withdrawals 31% occurred within 2 years of launch and 50% within 5 years. Analysis of the average lifetime of any drug also paints a worrying picture with the average drug lifetime being 12.3 years in the 70's, 6.6 years in the 80's and only 2.6 years in the 90's. Similarly, safety related label changes to lower the maximum dose followed this trend with 58 FDA enforced actions between 1980 and 1999.

The withdrawal of cerivastatin, an effective and clinically popular HMG-CoA reductase inhibitor, from the market due to rhabdomyolysis (31 fatal cases reported to date) associated with its use highlights the perils of drug-drug interactions that afflict many drugs during their routine clinical use. First approved in the USA and the European Union (EU) in 1997, the sponsor withdrew the drug from the market worldwide in August 2001, after a market life of just over 4 years.

Cerivastatin represents the most recent example in a long list of many valuable drugs that have been lost because of their drug interaction potential. Other drugs withdrawn from the market since 1993 due to drug interactions observed during their routine clinical use include sorufidine (1993), terfenadine (1998), mibefradil (1998), astemizole (1999), cisapride (2000) and levacetylmethadol (2001).

In the current context of P450-mediated metabolism and early drug safety, regulatory interest focuses on genetic modulation of these important drug metabolising enzymes with consequences for dose-response studies, drug interactions and extrapolation of data from one population to another. The International Conference on Harmonisation (ICH) guideline on 'Dose-Response Information to Support Drug Registration' refers to the role of polymorphic metabolism and pharmacological targets in determining dose-response. Of particular regulatory concern is the fact that many new chemical entities are often poorly characterised during their pre-approval phase for their interaction potential. Cerivastatin was thought to be primarily metabolised by CYP3A4 with minor contribution from other CYP isoforms. Since there were no interactions with inhibitors or substrates of CYP3A4 and CYP2C19, it was prescribed widely, very often concurrently with gemfibrozil. The dominant role of CYP2C8 in the metabolism of cerivastatin and its inhibition by gemfibrozil was not uncovered until after its withdrawal. Regulatory authorities in all the three ICH regions (EU, USA and Japan) have issued guidance notes to address all these concerns. Increasing globalisation of drug development programmes makes a compelling case for early characterisation of any

metabolic differences between the population investigated and the one targeted.

Conclusions

Drug safety will always play a key role in the development of any new drug. The improved understanding of toxicological and other safety mechanisms coupled with advances in the application of new technologies will allow the pharmaceutical industry to evaluate drug safety issues much earlier in their lifetime which will provide benefits to both the industry and the patient. This meeting provided a timely overview of the issues and opportunities facing today's drug discoverer with opinions from early in the drug discovery process right through to the regulatory process.

Do you know a student who could benefit from attending one of our conferences?

They can apply for a bursary.....

- Bursaries cover registration fee and make a generous contribution towards travel.

- Applicants are eligible for one bursary per year.

How to apply

- Visit www.socmr.org to download the application form.

- Complete form and appropriate registration document

- Secure a signature to confirm student status (eg Head of Department)

- Send it all to the Secretariat address on page 2

- Encourage students to apply early - there are five available for each meeting

Winners of the 2003 SMR Award for Drug Discovery



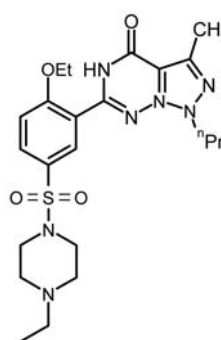
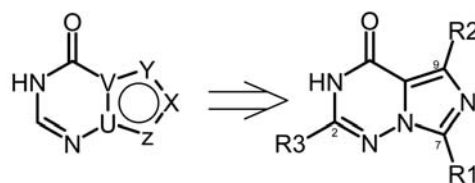
Dr Juerg Zimmermann, Dr Ulrike Pfaar and Dr Peter Graf, of Novartis, winners of the 2003 SMR Award for Drug Discovery, with the SMR Chairman, Dr Malcolm Duckworth, who presented the awards. Three of their award-winning colleagues (Dr Elisabeth Buchdunger, Dr John Ford and Dr Renaud Capdeville) were unable to attend the meeting. You can read about the Award winning lecture on Glivec, presented by Dr Zimmermann, on page 11.

Case Histories in Drug Discovery and Design

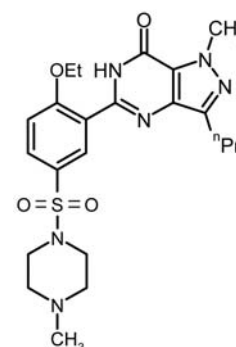
by The SMR Committee

The Society for Medicines Research (SMR) held a one-day meeting on case histories in drug discovery on December 4th 2003 at the National Heart and Lung Institute in London. These meetings have been organised by the SMR biannually for many years and this latest meeting of the proved extremely popular, attracting a capacity audience of over 130 registrants. The purpose of these meetings is educational; it allows those interested in drug discovery to hear key learnings from recent successful drug discovery programmes. There was no overall linking theme between the talks other than each success story has led to the introduction of a new and improved product of therapeutic use. The drug discovery stories covered in the meeting were extremely varied and, put together, emphasised that each successful story is unique and special. This meeting is also special for the SMR in that it presents its "SMR Award for Drug Discovery" in recognition of outstanding achievement and contribution in the area. Drug discovery is an extremely risky business and it has to be remembered that it is an extremely costly and complicated process where the success rate, is at best, low.

Dr Helmut Haning (Bayer Healthcare, Germany) opened the meeting describing the story behind the phosphodiesterase 5 (PDE5) inhibitor, Vardenafil, which is used to treat erectile dysfunction. PDE5 is characterised by its specificity for cGMP and allosteric binding sites for the substrate. It is known that suitably substituted purinones can behave as bioisosteres for cGMP and are potent PDE inhibitors. However, the team at Bayer demonstrated that although the purinones were potent *in vitro*, they lacked *in vivo* efficacy. The Bayer team hypothesised that substitution of the carbon atom for a heteroatom may increase the metabolic stability of the heterocyclic core. The imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones turned out to be the optimal heterocyclic core for inhibition of PDE5. Thus, Vardenafil was discovered and was determined to be at least an order of magnitude more potent than Sildenafil while also displaying greater selectivity with respect to PDE1. In addition to the heterocyclic core, the two molecules differ in the substituent on the piperazine nitrogen. It was clearly demonstrated that the superior potency is due to the change in the heterocycle, however, the potency enhancement observed cannot currently be explained through X-ray co-crystallisation analysis. Vardenafil is also more potent than Sildenafil in the conscious rabbit model of erectile dysfunction. Clinically, Vardenafil reaches its *T*_{max} early and is efficacious in over 90% of the patients. Side effects have been reported to be mild and transient.



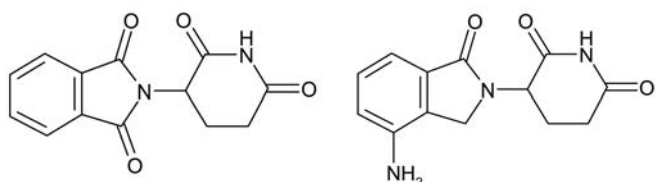
Vardenafil



Sildenafil

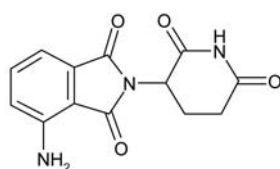
Dr George Muller (Celgene, USA) gave a presentation focussing on the history, current and future therapeutic indications for thalidomide. By the late 50's thalidomide had become a popular sedative but was removed from the market when its use as a treatment for morning sickness was linked to serious birth defects. The serendipitous discovery of its anti-inflammatory activity in the mid-60's for the treatment of erythema nodosum leprosum (ENL) in leprosy resulted in its renewed use. The discovery of thalidomide TNF- α inhibitory activity, anti-angiogenic activity and its clinical efficacy in cancer trials has resulted in renewed interest in thalidomide and its analogues. Celgene began development of thalidomide in 1992 and received FDA approval in 1998 for the treatment of cutaneous manifestations of ENL in leprosy. The major use of thalidomide in the US is now in oncology, with particular focus on blood cancers. A large number of clinical trials have demonstrated clinical efficacy of thalidomide in the treatment of multiple myeloma. Thalidomide is currently being investigated in over 140 clinical trials. Because the mechanism of action relating to the side effect profile was unclear, Celgene began a drug discovery program at the end of 1992 to discover thalidomide analogues with improved activity that lacked the side effects of teratogenicity, neuropathy, constipation and sedation. This research resulted in the discovery of a new class of thalidomide analogues termed IMiDsTM. The IMiDsTM are thalidomide analogues with greatly improved *in vitro* activity that show potent anti-inflammatory activity and anti-cancer activity. Revimid and Actimid are potent inhibitors of not only TNF- α (IC₅₀ > x2000 that of Thalidomide) but also a

range of cytokines and COX-2 induction. Like Thalidomide, the IMiDs also possess a chiral centre that rapidly epimerises. Importantly, none of the tetratogenic, sedating or constipating side effects observed with Thalidomide is seen with Revimid. It also displays excellent bioavailability in the rat, dog and monkey (>50%) and is currently in a number of early to late clinical trials.



Thalidomide
TNF- α , IC₅₀ >190 μ M

Revimid
TNF- α , IC₅₀ 100 nM

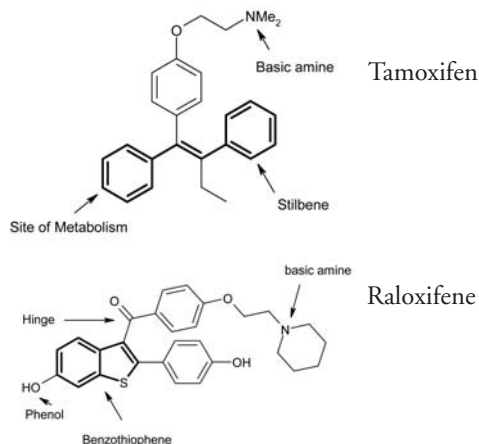


Actimid
TNF- α , IC₅₀ 13 nM

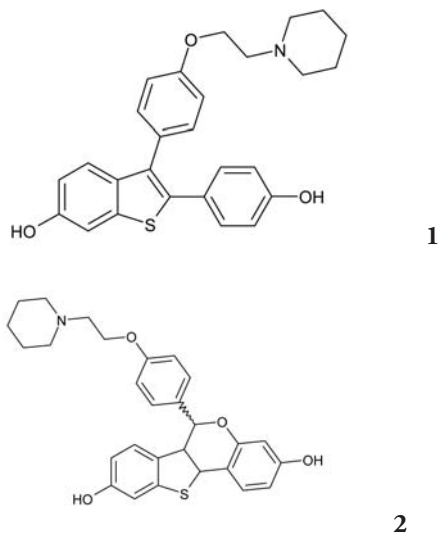
Dr Stan Vanboeckel (Organon, The Netherlands) took the audience on the journey focussing on the discovery and development of Arixtra, a story that involved the 50-70 step syntheses of a clinical candidate! Since 1936, heparin has been used in clinics for the prevention and treatment of thrombosis. Its main antithrombotic activity is in its ability to potentiate the activity of the serine protease inhibitor antithrombin III (AT-III), which inactivates a number of serine proteases such as thrombin and factor Xa in the coagulation cascade. From studies on heparin fragments it was deduced in 1981 that a unique pentasaccharide (PS) fragment, that occurs in about one-third of the heparin polysaccharide chains, constitutes the minimal binding domain for AT-III. The PS fragment (also known as the DEFGH part of heparin) was synthesised a couple of years later to confirm the earlier proposal. A key moment in the discovery of Arixtra was when it was recognised that a metabolically labile cyclic acetal could be stabilised via methylation giving a modified synthetic pentasaccharide fragment that was found to elicit a very selective antithrombotic mode of action. Interestingly, Organon and Sanofi arrived at the same molecule (ORG 31540/SR90107) and decided to collaborate. The results of four Phase III clinical trials demonstrated PS provides a

superior benefit over low molecular weight heparin in preventing deep-vein thrombosis (DVT) in major orthopaedic surgery patients, with an overall relative risk reduction of 50% and a similar safety profile. In 2002 the FDA approved this pentasaccharide as a new antithrombotic drug called Arixtra®. The specificity of the interaction of the PS with AT-III was confirmed when PS analogues were synthesised and tested for inhibition of blood coagulation factor Xa. SAR analysis established a simplified AT-III/PS interaction model. Introduction of an extra sulphate group at position 3 of unit H of the naturally occurring fragment gave an analogue that displayed higher affinity towards AT-III and an enhanced AT-III mediated anti-Xa activity. A simplified series in which all hydroxyl groups were methylated and in which all N-sulphate groups were replaced by O-sulphate groups gave several analogues (e.g. SanOrg34006) that were highly potent. SanOrg34006 binds much stronger to AT-III (K_d = 20nM), relative to the PS (K_d = 700 nM), and as a result its elimination half-life is much longer.

Dr Jeffrey Dodge (Lilly, USA) talked of the quest for selective estrogen receptor modulators for the treatment of postmenopausal osteoporosis. The first estrogen antagonist was discovered in the 1950's and tamoxifen (TAM, ICI) was later approved in 1973 for the treatment of breast cancer, although the therapy was later discontinued after it was found that TAM was a partial agonist in uterine tissue. This uterine agonist activity has been associated with an increased risk of endometrial cancer. The desire was to identify an agent that would antagonise the effects of estrogen on the mammary tissue while mimicking its effects on the bone. Interestingly, the geometrical isomers of TAM have opposing biological activities. It was hypothesised that structural changes to the ligand may influence the conformation of the receptor/ligand complex and thereby affect which estrogen responsive genes are modulated in various tissues. SAR analysis focused on varying the central template with particular attention on identifying a replacement for the stilbene scaffold. From this analysis, Raloxifene was identified in the early 1980's.



The biological activity of Raloxifene differs from that of TAM in that it is an antagonist in uterine tissue. Compounds **1** and **2** were prepared in order to establish whether the benzothiophene ring system and/or carbonyl "hinge" was responsible for the enhanced tissue selectivity.



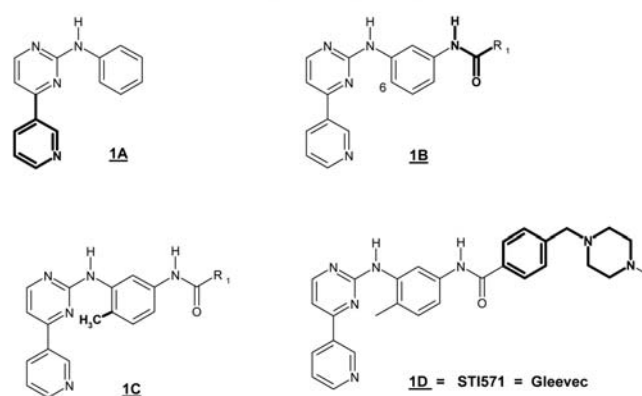
In compound **1** the hinge carbonyl has been removed, while in compound **2**, the orientation of the basic side chain has been rigidified by incorporation of the carbonyl into a benzopyran ring. Interestingly, while the *in vitro* estrogen action of compounds **1** and **2** were similar, compound **1** produced a significant increase in uterine eosinophilia and uterine weight. The hydroxylation pattern was important for receptor binding and *in vitro* activity, and the presence and nature of the basic side chain critical for determining estrogen antagonist activity. The shift from an acyclic olefin in TAM to a benzothiophene system in Raloxifene is the most striking structural difference between the two molecules. Dodge and co-workers proposed that it was this modification, together with the inclusion of a carbonyl "hinge" that were responsible for the differences in tissue selectivity observed between TAM, Raloxifene and compounds **1** and **2**. Modelling studies suggested that these simple modifications produce a dramatic change in the position of the basic side chain from a nearly orthogonal orientation in Raloxifene to a coplanar orientation for TAM. Thus it was hypothesised that the coplanar orientation of the side chain of TAM and compound **1** were responsible for the uterine stimulation observed.

The 2003 SMR Award for Drug Discovery was presented to the key members of the team that led to the discovery of Gleevec (STI571), developed for the treatment of chronic myeloid leukemia (CML). Juerg Zimmermann, Elisabeth Buchdunger, Ulrike Pfaar, Peter Graf, John Ford and Renaud Capdeville, key scientists from the Novartis programme team. Dr Juerg Zimmerman delivered the Award lecture. Until recently a patient suffering from CML, a cancer of the blood

cells, had few options. Radiation, the first treatment for CML, was introduced in the 1920s. Chemotherapeutic agents followed in the 1950s and 1960s. Superior to radiation therapy, chemotherapy increased survival among patients with CML to about five years. Bone marrow transplantation arrived in the 1970s, and interferon-alpha debuted in the 1980s. Of all these treatments, only bone marrow transplantation currently provides a potential "cure", that is, long-term remissions from cancerous cell growth. Gleevec represents a remarkable story that began more than 40 years ago with the discovery of the Philadelphia chromosome, the first cancer-related genetic abnormality to be recognised. The discovery hinged on the clarification of the role of Bcr-Abl in CML, which later provided Novartis with the unique opportunity to discover and develop this targeted anticancer therapy.

The Novartis discovery of Gleevec started with a desire to discover potent, selective and orally active ATP-competitive protein kinase inhibitors, based on a central phenylamino-pyrimidine template. This scaffold was thoroughly optimized eventually leading to compounds with potent activity against Protein Kinase C (PKC). Excellent cellular activity was obtained with analogues bearing a 3'-pyridyl group at the 3-position of the pyrimidine (1A). During the optimization of this structural class on the inhibition of PKC, a serine/threonine kinase, it was observed that the presence of an amide group on the phenyl ring also gave rise to inhibition of tyrosine kinases, such as the bcr-abl kinase (1B). In this case the amide bond was required to be stable to exclude potential toxicological issues. High hydrolytic stability could be achieved with derivatives with R¹ = phenyl. Selectivity was the next hurdle since these compounds inhibit PKC as well as tyrosine kinases.

Optimization of the Phenylamino-Pyrido-Pyrimidine Lead Structure



A key observation was made from SAR in that substitution at position 6 of the diamino phenyl ring was not tolerated for PKC inhibition and introduction of a simple 'flag-methyl' led to loss of activity against PKC, while the activity against protein-tyrosine kinases was retained (1C). Disappointingly, the first series of selective inhibitors prepared showed low aqueous solubility and poor oral bioavailability. This drawback was circumvented by the introduction of a solubilising side chain in a region of the molecule, which did not interfere with the binding affinity. This modification increased the aqueous solubility and the oral bioavailability. The attachment of basic groups at 4-position of the phenyl ring raised an "aniline-alert" (mutagenic potential) which was avoided by the introduction of a spacer between the phenyl-ring and the nitrogen-atom. The best compound from this series was the methyl-piperazino derivative, STI571, which was selected as the most promising candidate for clinical development (1D). STI571, eventually known as Gleevec, was the first protein kinase inhibitor to reach the market and also the first example of a targeted drug therapy for cancer. Gleevec won approval from the US FDA on May 10, 2001 for the treatment of chronic myeloid leukemia after a lightning-fast 2-½ month review. It represents a monumental leap forward in cancer chemotherapy and demonstrates that highly specific, non-toxic therapy is possible. It does not guarantee success of similar efforts because CML may not be typical of most other malignancies. Congratulations to the Novartis team for accomplishing the equivalent of the four-minute mile.

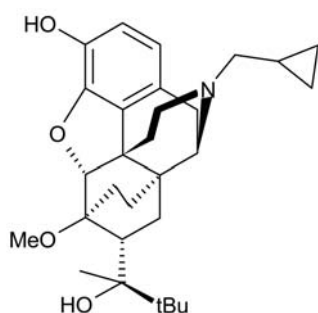
Dr Howard Fox (Novartis, UK) focused on the developmental issues overcome along the journey to the discovery of the antibody, Xolair, a first in class treatment for asthma. Developments in the anti-inflammatory treatment of asthma currently provide patients with more choices for reducing and controlling the symptoms associated with the disease. Inhaled corticosteroids, prescribed since the 1980's, help control airways inflammation and inhaled short-acting B2 receptor agonists provide symptom relief for asthma patients. Since then, incremental advances in asthma treatment have led to the development of inhaled long-acting B2 agonists and oral leukotriene antagonists. Despite these advances, asthma remains a heavy financial and social burden for many of the +3 million UK patients. Omalizumab is the first recombinant DNA-derived humanised monoclonal antibody developed to intervene in the critical common pathway of pathophysiological expression of asthma and allergy, namely immunoglobulin E (IgE). Omalizumab consists of a humanised IgG1 framework (95%) with a variable murine antibody sequence (5%) grafted onto the framework. This avoids any potential sensitisation to murine antibodies, as they are not detected by the human immune system when Omalizumab binds to the IgE. Omalizumab was also designed to be nonanaphylactogenic due to the fact that it is

unable to bind to IgE already bound to the high affinity IgE receptors of mast cells. Omalizumab binds to free IgE, forming a biologically inert complex that is unable to bind to effector cells, therefore blocking the allergic response of asthma. By adjusting Omalizumab's dose according to body weight and IgE levels, IgE can be reduced by upto 95%; this also leads to a down regulation of the high affinity IgE receptors on basophils and, potentially, mast cells. The results from clinical trials of more than 6,000 patients indicate that treatment with Omalizumab reduces asthma exacerbations, time to exacerbation, inhaled corticosteroid use, rescue medication use, asthma symptom scores and healthcare utilisation. Omalizumab was approved in Australia in 2002 and in June 2003 the US FDA licensed Xolair (Omalizumab) for the treatment of adolescents and adults with allergic asthma.

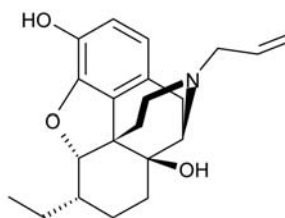
The final lecture of the meeting focused on emerging treatments for opioid dependence and was delivered by a former SMR chairman, Dr Chris Chapleo (Reckitt Benckiser Healthcare, UK). Efforts to tackle the problems associated with opiate (heroin) addiction are driven by the recognition of a need for effective Harm Reduction policies. This encompasses a range of activities and issues including health and risk behaviours from transmission of HIV and hepatitis, criminal behaviour and social functioning. Maintenance therapy (also referred to as substitution therapy) has a clear role to play in any programme aimed at reducing harm associated with addiction. Methadone, as a once a day therapy, has been the maintenance therapy of choice for over 30 years. Unfortunately, methadone is also highly addictive, resulting in overdose situations and it is also very difficult to achieve a state of abstinence due to severe withdrawal problems. Even if patients successfully reduce their dose until they reach the drug free state it is estimated 90-95% of patients relapse. Buprenorphine's potential as a treatment for heroin addiction was first recognised during the 1970's. Discovered in 1966, buprenorphine was developed as a potent analgesic of the morphine class in 1978, from which time effort focussed on buprenorphine's potential as a new indication for Addiction Treatment. Its unique qualities result from it being a partial agonist at the μ receptors in the brain. Other agents acting at this receptor (heroin, morphine, and methadone) are full agonists producing very high levels of physical dependence. The physical dependence of buprenorphine has been evaluated in rodents, dogs and monkeys, and is markedly lower than that of full agonists. Current evidence supports the theory that the low level of physical withdrawal following chronic buprenorphine treatment is due to slow receptor kinetics. Therefore when drug administration is stopped after chronic dosing buprenorphine leaves the receptors very slowly such that the biochemical systems involved in the dependence process return to their pre-treatment levels whilst maintaining homeostasis.

With the full agonists, opiate withdrawal results in an abrupt return of the system to predependence levels and this is responsible for "spontaneous withdrawal". Buprenorphine also possesses an improved safety profile. In a dose ranging study with sublingual doses of 1-32 mg a non-statistical decrease in respiration rate at the 4 mg dose level was observed; thereafter no further decrease in respiratory rate was observed as the dose increased. Blood levels increased over this dose range; thus decreased absorption was not a possible reason for decreased effect on respiration. Tolerance is another aspect of full agonists that is a major concern in addiction treatment, where addicts over a period of time have to consume higher levels of their opiate to achieve the same effects. Addicts who have stopped "consumption" are in danger if they return to their habit using the same dose level used prior to the period. Buprenorphine does not suffer from this tolerance problem which in effect is a measure of its safety. As with all opiates, buprenorphine has been the subject of abuse by the injectable route and diversion of products containing buprenorphine has occurred in a number of countries. Naloxone is a competitive μ antagonist and produces an opioid withdrawal syndrome when administered intravenously to an opioid dependent individual.

However naloxone is not well absorbed when administered sublingually and it has been shown that it does not interfere with buprenorphine's absorption or pharmacological effects when administered in combination by the sublingual route. The optimum ratio of buprenorphine and naloxone in a combination product is 4 to 1 and this combination is sufficiently unpleasant to the opioid dependent individual who might abuse the product, but it does not attenuate the "good" opioid agonist effects. Taken sublingually the combination product Suboxone, is equivalent to the buprenorphine alone product Subutex. However, if abused intravenously the combination product precipitates withdrawal in opioid dependents and is perceived to be naloxone by those who inject the product. New dosage formulations were essential to clinically probe the safety and efficacy of buprenorphine and to determine the dose range for treatment. As buprenorphine is not orally active, a number of routes of administration have been examined and for convenience a sublingual liquid has been developed.



Buprenorphine, μ -partial antagonist



Naloxone, μ -antagonist

Animal Research and Public Opinion by Mark Matfield

The use of animals in research and testing is probably the oldest and most entrenched public debate about any aspect of science. The first anti-vivisection organisation was founded (in the UK of course) in 1863. The scientific community was slow to respond, but in 1908 the Research Defence Society was formed to be their voice in that debate. Its main objective was to inform the public about the importance of animal experimentation for medical progress. Currently, we would define our main objective as communicating with the public about animal research, because we have learned that this is not a simple matter of telling people how essential it is.

The communications activities of the RDS can be divided into two main areas. We produce a large amount of material for direct communication, such as leaflets, posters, adverts, videos and our web site. However, the most effective means of communicating with the public at large is via the media, so a lot of our time is spent working with journalists. The fact that the RDS is the oldest and best-known organisation representing the scientific position on animal experimentation is a considerable advantage to us, because most journalists have either heard of us or find out about us very soon after they start working on a story concerning animal research. This means that they normally contact the RDS at an early stage.

Over the years, RDS has built a considerable expertise at dealing with the media on this complex and frequently emotive subject. By using professional monitoring services we have recorded and analysed all media coverage of animal experimentation for the last thirteen years. That analysis shows a very clear change in the way that the media have covered the issue. In the early 1990's the vast majority of media coverage was partisan - it was either for or against animal experimentation. However, over the following five years there was a rapid growth in the number of factual reports about animal research until, by the late 90's the majority of reporting was of this type. Typically, these were reports of examples of progress in medical research that explicitly mentioned that the progress had come from animal experiments. Often the animals were mentioned in the first or second paragraph of the article.

The public receive very different messages from these two types of media coverage. When it comes to subjects like animal experimentation, the public do not place greater faith in information coming from scientists than in information from other sources. So, if the majority of the press coverage that they saw was either for or against animal experimentation, the impression they received was simply that there was a debate about the subject. Ergo, animal experimentation was a debatable subject.

However, the factual reporting of animal experimentation sent a completely different message to the public. From these reports, the readers took home the message that medical progress depends on animal research, with no debate or equivocation. The shift in the media coverage of this issue during the 90's appears to have resulted in a significant change in the information the public were receiving about this issue and, as a result, a change in their attitude towards it.

This shift in public attitudes has been explored by several recent projects that were conducted to analyse public attitudes to the use of animals in research. These have revealed that the public has a rather sophisticated attitude to this issue. Rather than simply being for or against it, people tend to view it with an attitude that has been called 'conditional acceptance'. The conditions they place upon their acceptance are: a) that the research is done for an important medical purpose, b) that animal suffering is minimised or eliminated and c) that alternative methods are used whenever possible. If those conditions are satisfied, the vast majority of the public are willing to accept animal research. This finding has been confirmed in three separate studies. Indeed, these studies, which were conducted between 1999 and 2002 suggested that the percentage of people who were 'conditional accepters' increased from 85% to 90% during this period.

Over the same period, there were noticeable shifts in public trust about animal experimentation. Public trust is a very important aspect of this issue. Since the vast majority of people are conditional accepters, they do not need to be told that animal experimentation is necessary for medical progress. Their main concerns are about how it is done, not whether it is necessary. The scientific community and the government can tell the public that animal experimentation is conducted properly, working to high welfare standards and for important research, but the crucial question is whether the public will believe them. This is why levels of public trust are so important.

The research studies conducted between 1999 and 2002 specifically measured public trust in various groups as a source of accurate information about animal experimentation. The results of these studies are expressed as net trust ratings, which are

simply the percentage of people saying they trust a source minus the percentage who say they do not trust a source. In 1999, antivivisection groups had a net trust rating of 19%, scientists only had a rating of 16%. However this shifted dramatically over the next three years and by 2002 the net trust in antivivisection groups had fallen to 9% and in scientists had increased to 26%.

In addition to our public communications activities, RDS also devotes a significant amount of effort to political lobbying. Currently, the scientific community has a higher level of government support on the issue of animal research than at any time in the past. Over the last few years we have seen strong statements in support of animal research from a number of Ministers, including the Prime Minister, and firm government action to introduce new legislation to deal with animal rights extremism. One might be tempted to assume that this means we no longer need to devote much effort to matters political. In fact, we now devote more time and effort to working with the government than we used to devote to lobbying them.

There are two broad issues that need government action: a) dealing with animal rights extremists and their effects and, b) reducing the burden of bureaucracy on animal research. Both are complex issues. The government's action to restrict the activities of animal rights protesters will affect all protesters. So far, they have not met any significant opposition from the civil rights movement, but they are aware of the need to tread carefully in this area. The pressure to increase the burden of bureaucracy on animal research comes from within government - principally from the Home Office, so any initiatives to limit that burden pit one government department against another. Once again, this is something that requires careful handling.

The changes in public and political attitudes to animal research that we have seen in recent years would have been difficult to predict a decade ago. The task before us now is to translate those shifts in attitude to more concrete and long-term safeguards for animal-based medical science in the UK.

**Dates for your diary
Forthcoming SMR Symposia 2004**

Chemokines Receptors and Drug Discovery

March 11, 2004

**Novartis Horsham Research Centre, Wimblehurst Road, Horsham,
West Sussex**

Diabetes

June 17, 2004

National Heart & Lung Institute, London

Removing the Constraints to CNS Drug Discovery and Development

September 9, 2004

National Heart & Lung Institute, London

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